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EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 12/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,605	KOKEN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) 12,15-19,21 and 24-33 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 12,15-19,21 and 24-33 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 13 and 14 have been canceled. Claims 12, 15, 19, 21 and 24 have been amended. Claims 26-33 have been added. Claims 12, 15-19, 21 and 24-33 are pending and under consideration.

Text of Title 35, U.S. Code, not found in this action, can be found in a prior action.

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear how claim 18 further limits claim 12. Claim 18 recites the method of claim 12 wherein a) and b) are administered simultaneously or sequentially. The only two options for the administration of a) and b) in claim 12 are simultaneous or sequential. Thus, it appears that claim 18 has the same scope as claim 12.

Claims 12, 15, 18, 21, 25-28, 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12, 15, 18, 21, 26-28, 31 and 32 are drawn to method claims reliant on the identity of "an agent which induces the over expression of the PML protein". Thus the claims encompass a genus of "agents" which are responsible for evoking the over expression of the PML protein. The genus is highly variant because it includes any molecule having the ability to cause over expression of the PML protein. This is in contrast to the specification which identifies only interferons as capable of evoking said over expression. The description of interferons does not adequately describe the genus of "agents" encompassed by the claims because said agents are not limited in terms of structure to the interferons. Claim 25, when given the broadest reasonable interpretation encompasses a genus of inhibitors of any caspase. Although drawn to DNA arts, the findings in University of California v. Eli Lilly and Co., 119

F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and Enzo Biochem, Inc. V. Gen-Probe Inc. are relevant to the instant analysis of adequacy of written description. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. At 1567, 43 USPQ2d at 1405. The court also stated that a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. Id. At 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id. In the instant case, the genus is of agents which induce over expression of PML and the genus of caspase inhibitors is described only by function, that is, the ability to induce the over expression of PML and the ability to inhibit any caspase. It logically follows that if the product on which a method claim is based is not adequately described, the method itself is also not adequately described.

Claims 24, 25 and 33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in

Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The instant claims are drawn to a stimulation of an immune reaction in a patient comprising administering to said patient a caspase inhibitor in combination with an interferon. Claims 25 and 33 specify the caspase inhibitors of zVAD and DEVD, respectively. When given he broadest reasonable interpretation, claim 25 encompasses an inhibitor of any caspase.

The post-filing date art (Quignon et al, Nature Genetics, 1998, Vol. 20, pp. 259-265, reference of the IDS filed July 26, 2001) teaches that arsenic and zVAD enhance PML and IFN-induced apoptosis. The specification specifically teaches that the exposure of cells over expressing the PML protein to arsenic in combination with interferons, or zVAD or DEVD (page 17, lines 18-19) causes a type of cell death which does not exhibit characteristics typical of apoptosis , such as condensation of chromatin and nuclear fragmentation (page 7, lines 10-14 and 20-21). It is noted that the specification is mute about the integrity of the plasma membrane, a feature which is a defining characteristic of necrosis Quignon et al teach that PML-mediated cell death is a central and unexpected cell death pathway which is independent of caspases (page 264, first column, lines 12-15 and lines 32-37, under the heading "A novel and central cell death pathway?"). Quignon et al teach the characteristics of this death pathway to include cytoplasmic shrinkage, appearance of sub-G1 DNA, membrane phosphatidly serine externalization and loss of mitochondrial transmembrane potential (page 260 first column, lines 10-17). Quignon et al specifically note that the cells retained the ability to exclude trypan blue (page 260, first column,

lines 17-18). Quignon et al conclude that although DNA cleavage was occurring as evidence by the presence of sub-G1 DNA, internucleosomal DNA laddering was not observed (page 260, first column, lines 21-25). These findings are consistent with those reported in the specification. Perry et al (Biotechniques, 1997, Vol. 22, pp. 1102-1106) teach that although membrane permeability is characteristic of necrosis and DNA fragmentation is characteristic of apoptosis, the oligonucleosomal degradation of DNA is not a prerequisite for apoptosis (page 1102, second column, lines 46-51) and that some cells exhibit morphological features of apoptosis within any DNA fragmentation (page 1103, first column, lines 1-4). It can be reasonably concluded that the PML-induced cell death pathway, although not a "typical" apoptotic death pathway, is not a necrotic death pathway because membrane integrity is preserved as is evident by the exclusion of trypan blue dye. Lutz et al (Trends in Immunology, 2002, Vol. 23, pp. 445-449) teach that only fully mature dendritic cells are able to induce an immune response, and that semi-mature or immature dendritic cells , when confronted with antigen induce tolerance (abstract, lines 4-7). Sauter et al (Journal of Experimental Medicine, 2000, Vol. 191, pp. 423-433) teach that necrotic tumor cells, in contrast to apoptotic cells induce maturation of dendritic cells (page 430, first column, lines 3-9). Neither the specification, nor any art of record supports necrosis as a cell death pathway mediated by the PML protein. Thus, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to use the claimed methods to the extent that they read on the stimulation of an immune response.

Claims 12, 15-19, 21 and 24-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inducing the death of undesirable leukemia cells comprising administering interferons which induce the over expression of PML in combination with arsenic trioxide, zVAD or DEVD, does not reasonably provide enablement for methods of inducing the death of non-leukemic undesirable cells, or methods requiring the adminsitration of the PML protein rather than an interferon, or methods requiring the adminsitration of an "agnet" which is not interferon. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims are drawn to methods of inducing the death of undesirable cells comprising the administration of arsenic trioxide, zVAD or DEVD in combination with the PML protein or an agent which includes the over expression of the PML protein.

(A) as drawn to a method of inducing the death of "undesirable cells"

The specification teaches that in APL, the PML protein is not located on the nuclear bodies by delocalized because of the expression of the PML-RARalpha fusion protein. The specification teaches that treatment of APL cells with Arsenic trioxide cause the return of the PML protein to its normal location with a concomitant death of the cells. The specification notes tat in normal non-APL cells, wherein the location of PML is normal, arsenic induces the aggregation of the PML protein into large modified bodies but that this aggregation does not result in cell death (page 1, line 22-29). The art corroborates the teachings of the specification in that in Promyelocytic Leukemia the expression of the RAR alpha disrupts the nuclear bodies resulting in a diffuse pattern of PML localization (Lallemand-Breitenbach et al, Journal of Experimental Medicine, 2001 Vol. 193, pp. 1361-1371). Neither the art, nor the specification, teach "undesirable cells" other than APL cells which have ectopic expression of the PML protein, which when exposed to an agent which corrects this expression, such as arsenic trioxide, zVAD or DEVD in combination with an interferon which induces the over expression of the PML protein, results in death of the cell. In order to practice the invention to the full scope of the claims, it would be necessary to identify other "undesirable cells" exhibiting ectopic expression of the PML protein which can be reversed by the administration of arsenic trioxide, zVAD or DEVD. It is noted that no other "undesirable cells" having the aforesaid characteristics are known as of the current year, in contrast to the earliest priority date sought for the instant application. One of skill in the art would be subject to undue experimentation without reasonable expectation of success to identify "undesirable cells" other than APL cells in which death can be induced by the instant invention.

(B)As drawn to the administration of the PML protein.

Claims 12, 15, 18 and 26-28 require the death of undesirable cells in a patient. The art teaches that PML is a structural protein associated with the nuclear matrix and constitutes the scaffold component of the nuclear bodies (Takahashi et al, Oncogene, 2004, Vol. 23, pp. 2819-2824). In order for the administration of the PML protein to have an efficacious effect on a

patient when administered in vivo, it would be necessary for the administered PML to penetrate the plasma membrane of an undesirable cell and then penetrate the nuclear envelope thereof, followed by integration into the nuclear matrix. The art teaches that the direct intracellular delivery of proteins or peptides is difficult due to the plasma membrane of the cell which prevents the uptake of macromolecules by limiting passive entry (Wadia and Dowdy, Advanced Drug Delivery Reviews, 2005, Vol. 57, pp. 579-596, especially page 581, first column, first full paragraph). The art teaches that this problem can be overcome by attachment of peptides and proteins to protein domains having cell membrane penetrating ability and identified the Drosophilae antennapedia protein as one such protein which was known in the art before the instant filing date (Wadia and Dowdy, ibid, page 581, first column, lines 26-31) . However, the instant invention would necessitate the proper localization of PML in the nucleus requiring not only the penetration of the plasma membrane followed by the additional penetration of the nuclear membrane. There are no teachings in the art or in the specification for how to treat and individual having cancer in such a manner as the administered peptides would traverse the plasma membrane of tumor cells and traverse the nuclear envelope as well. The art teaches that the nuclear envelope differs in structure from that of the plasma membrane and that larger proteins are transported across the nuclear envelop by saturable pathways that are energy-and signal-dependent which include nuclear localization sequences which (NLS) are commonly short stretches of amino acids rich in basic amino acid residues (Guo et al, WO 02/18572, page 3, lines 8-11). Thus, it appears as if the requirements for transversing the plasma membrane and penetrating the nuclear envelope are different as a result of the different structure of each. The specification provides no teachings as to the penetration of both the plasma membrane and the nuclear envelope of a tumor cell and the delivery of a quantity of the PML in such amounts as to be efficacious to a patient.

The art also teaches general problems with the administration of protein drugs, namely short half-life in vivo, necessitating multiple administrations (Johnson and Tracey, 'Peptide and Protein Drug Delivery', In: Encyclopedia of Controlled Drug Delivery, Vol. 2, 1999, pages 816-833). The art teaches that major stability, release and manufacturing challenges" (page 816, second column, lines 1-5) must be met in order to overcome the technical difficulties associated with the delivery of proteins in vivo. The specification does not teach a means for the delivery

of the PML protein to the appropriate site and the efficacious uptake to result in the death of undesirable cells in a patient. Therefore it would be undue experimentation in order for one of skill in the art to determine the means by which the disclosed peptides could penetrate both the plasma membrane and the nuclear envelope in a manner which still maintains the ability of said PML protein to function in the recruitment of proteins to the nuclear bodies, and then determine a means for the delivery of the peptides to the tumor in a patient in such quantities which would be efficacious to said patient, wherein said delivery means would include how to stabilize the peptides from degradation in vivo, or during the manufacturing process, and how to release the stabilized protein in vivo in the appropriate quantities. Given the lack of teachings on all of the above, one of skill in the art would be subject to undue experimentation in order to make and use the instant invention.

The rejection of claims 12, 16-19 and 21 under 35 U.S.C. 103(a) as being unpatentable over He et al (Anticancer Research, 1997, Vol. 17, No. 5C, page 3927, abstract #6) in view of Muller et al (EMBO, Jan 2, 1998, vol. 17, pp. 61-70) and Chelbi-Alix et al (NATO ASI Series H: Cell Biology (1996, Vol. 99 (Tumor Biology), pp. 17-27) is maintained for reasons of record. New claims 26 and 27 are also rejected for the same reasons of record.

He et al teach the administration of retinoic acid, IFN, arsenic trioxide , melarsoprol, or combinations thereof in transgenic models of APL. He et al do not specifically teach the combination of IFN and arsenic trioxide, or IFN and melarsoprol.

Muller et al teach that the post-translational modification of PML with SUMO-1 modulates the intracellular location of PML. Muller et al teach that arsenic trioxide increases the amount of PML-1-SUMO-1 conjugates that accumulate in the nuclear bodies. Muller et al teach that when ATL cells are exposed to arsenic trioxide PML-RARalpha is rapidly degraded but PML is not degraded (page 68, first column, lines 28-30). Muller et al teach that the kinetics of restoration of nuclear bodies is a direct consequence of PML-RARalpha destruction. Muller et al do not teach the molecular consequences of the administration of arsenic trioxide and interferon.

Chelbi-Alix et al teach that the PML/RARalpha fusion protein has been identified in acute promyleocytic leukemia, wherein the chimeric protein s a product of a t(15;17)

translocation rendering RARalpha under control of the PML promoter. Chelbi-Alix et al teach that the PML/RARalpha fusion protein contains the functional domains of both PML and RARalpha and is the likely molecular basis of APL leukaemogenesis probably through alteration of PML and/or RARalpha functions (page 19, lines 1-13). Chelbi-Alix et al teach that in APL the PML/RARalpha fusion protein displaces the PML protein into microspeckeles rather than the normal location of nuclear bodies. Chelbi-Alix et al teach that the microspeckles are smaller and much more numerous than the speckled nuclear bodies (page 19, lines 15-25). Chelbi-Alix et al teach that IFNalpha treatment of NB4 cells increases the micropunctuate pattern of PML and PML/RARalpha without altering their abnormal microspeckled location (without restoring the nuclear bodies) (page 21, lines 9-11). Chelbi-Alix et al teach that because IFNalpha increases PML/RARalpha in addition to PML, treatment with IFNalpha may enhance binding to RXR resulting in a further impairment of retinoic acid receptor function, which would act to increase the differentiation block toward nuclear receptors (page 21, line 12 to page 22, line 2). Chelbi-Alix et al teach that the demonstration that IFNalpha induces PML/RARalpha in APL cells is consistent with observations that the use of interferon in the treatment of APL can accelerate a patients leukemia (page 22, lines 7-10). Chelbi-Alix et al teach that over expression of PML retards cell growth and PML sharply reduces the transforming effects of cooperating oncogenes and suppresses transformation by activated neu oncogene (page 23, line 4 to page 24, line 2). Chelbi-Alix et al conclude that IFN-induced PML protein has anti-oncogenic effects (page 24, lines 2-3).

It would have been prima facie obvious to one of skill in the art to combine arsenic trioxide with interferon for the treatment of leukemias associated with the fusion protein PML/RARalpha, or for the in vitro inhibition of said leukemia cells. One of skill in the art would be motivated to do so by the teachings of Muller et al on the selective degradation of the PML/RARalpha fusion protein after exposure of HTLV-1 associated ATL cells to arsenic trioxide; and the teachings of Chelbi-Alix on the anti-oncogenic effects of the PML protein and the induction of both the PML and PML/RARalpha proteins by exposure of APL cells to interferon alpha. One of skill in the art would have concluded that while the effects of arsenic trioxide on the selective degradation of the PML/RARalpha fusion protein are desirable, the addition of interferon would be t least additive in effect because it would be expected that the

induction of PML would exert an anti-oncogenic effect and the concomitant induction of PML/RARalpha would be neutralized by arsenic trioxide degradation. Thus, one of skill in the art would expect that leukaemogenesis would be reversed by the decrease or elimination of PML/RARalpha and the increase in PML.

Applicant argues against the obvious ness of the combination of references and maintains that even if it were obvious to combine, the synergism afforded by the combination would not have been obvious. This has been considered but not found persuasive, because applicant is arguing limitations which are not in the claims. The death of undesirable cells can be effected by two agents which have an additive effect as well as a synergistic effect.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
11/28/2005

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